PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 September 2000 (11.09.00)	
International application No. PCT/GB99/04200	**Applicant's or agent's file reference** P15700WO
International filing date (day/month/year) 17 December 1999 (17.12.99)	**Priority date** (day/month/year) 19 December 1998 (19.12.98)
Applicant LECHLER, Robert, Ian et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 July 2000 (06.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Maria Victoria CORTIELLO
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
ROYAUME-UNI

Date of mailing (day/month/year) 11 August 2000 (11.08.00)	
Applicant's or agent's file reference P15700WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB99/04200	**International filing date** (day/month/year) 17 December 1999 (17.12.99)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

HARRISON GODDARD FOOTE
Belmont House
20 Wood Lane
Leeds LS6 2AE
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: 0113 225 8350

Facsimile No.: 0113 230 4702

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address

HARRISON GODDARD FOOTE
Tower House
Merrion Way
Leeds LS2 8PA
United Kingdom

State of Nationality:

State of Residence:

Telephone No.: +44 113 290 1400

Facsimile No.: +44 113 244 2829

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Maria Victoria CORTIELLO Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003461950

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
Harrison Goddard Foote
Belmont House
20 Wood Lane
Leeds LS6 2AE
UNITED KINGDOM

19.JUN.2000*050884

Applicant's or agent's file reference P15700WO	Date of mailing *(day/month/year)* 15/06/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 99/04200	International filing date *(day/month/year)* 17/12/1999
Applicant ML LABORATORIES PLC et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Nina Vercio

Form PCT/ISA/220 (July 1998)

TES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P15700WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/04200	17/12/1999	19/12/1998
Applicant		
ML LABORATORIES PLC et al.		

19.JUN.2000*030885

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

IMPROVEMENT OF TOLERANCE TO A XENOGRAFT

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04200

Box I Observations where certain claims were found unsearchabl (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04200

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/00 A61K39/385 C07K16/28 G01N33/577 G01N33/68
A61P37/06 //C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 11971 A (ALEXION PHARMACEUTICAL INC.) 3 April 1997 (1997-04-03) 'summary of the invention', especially paragraph 5.	16-19
Y		1-18, 20-23
Y	T. LOGTENBERG ET AL.: "Autoreactive B cells in normal humans." THE JOURNAL OF IMMUNOLOGY, vol. 140, no. 2, 15 January 1988 (1988-01-15), pages 446-450, XP002139205 Baltimore, MD, USA the whole document	1-18, 20-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2000	15/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04200

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. DORLING ET AL.: "T cell-mediated xenograft rejection: specific tolerance is probably required for long term xenograft survival." XENOTRANSPLANTATION, vol. 5, no. 4, November 1998 (1998-11), pages 234-245, XP000907182 Copenhagen, Denmark page 240, left-hand column, line 45 -right-hand column, line 44 ---	1-23
A	A. DORLING ET AL.: "Glaxo/MRS Young Investigator Prize. Xenotransplantation: immune barriers beyond hyperacute rejection." CLINICAL SCIENCE, vol. 93, no. 6, December 1997 (1997-12), pages 493-505, XP000907185 London, GB page 503, right-hand column, line 1 - line 14 ---	1-23
A	E. ELWOOD ET AL.: "Prolonged acceptance of concordant and discordant xenografts with combined CD40 and CD28 pathway blockade." TRANSPLANTATION, vol. 65, no. 11, 15 June 1998 (1998-06-15), pages 1422-1428, XP000906866 Baltimore, MD, USA the whole document ---	1-23
A	S. MAHER ET AL.: "Porcine endothelial CD86 is a major costimulator of xenogeneic human T cells." THE JOURNAL OF IMUNOLOGY, vol. 157, no. 9, 1 November 1996 (1996-11-01), pages 3838-3844, XP002139206 Baltimore, MD, USA the whole document -----	1-23

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04200

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-6 and 20-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/GB 99/04200

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9711971 A	03-04-1997	AU 7378096 A	17-04-1997
		CA 2232937 A	03-04-1997
		EP 0866807 A	30-09-1998

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PATENT COOPERATION TREATY

PCT

REC'D 02 APR 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P15700WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/04200	17/12/1999	19/12/1998
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant ML LABORATORIES PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/07/2000	29.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hinchliffe, P Telephone No. +49 89 2399 8431

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/04200

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-40	as originally filed				

Claims, No.:

1-23	as received on	27/11/2000	with letter of	24/11/2000	

Drawings, sheets:

1/39-39/39	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-6,19-23 with respect to I.A..

because:

   ☒ the said international application, or the said claims Nos. 1-6,19-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-15,18,20-23

	No:	Claims	16,17,19
Inventive step (IS)	Yes:	Claims	1-15, 20-23
	No:	Claims	18
Industrial applicability (IA)	Yes:	Claims	7-18
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

ITEM III

1. Claims 1-6,19-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

ITEM V

1. For the assessment of the present claims1-6,19-23 on the question of whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.1 D1 (as cited in the ISR) discloses the use of monoclonal antibodies, raised against porcine VCAM, to block the binding of VCAM with VLA-4 (see p.36, lines 24-30). The antibodies are shown to be specific for porcine VCAM and not the human homolog (see p.37, lines 2-12). Furthermore claims 16-17 are not rendered novel D1 by the term:

"which has less than 75% sequence homology to the equivalent human polypeptide".

as it is considered that the antibodies raised in D1 to porcine VCAM, P-selectin and CD86 could bind to antigens which have less than 75% homology with the human protein. There is no reason to suspect therefore that the antibodies of D1 are any different to those currently claimed. The inclusion of this definition does not therefore overcome the objection under Article 33(2) PCT made against claims 16 and 17.

2.2. Claim 19 is dependent upon claims 16-18 and it is considered not to be novel. The arguments made in point 1.1 above in conjunction with claim 3 of D1 deprive the subject matter of novelty (Art.33(2) PCT).

3. The subject matter of claim 18 is not inventive contrary to the requirements of

Article 33(3) PCT. D1 does not discloses direct labelling of the antibodies. Instead indirect labelling using FITC labelled goat anti murine Fc antibodies are used. It is considered that the alternative method of labelling covered by this claim is not surprising or inventive.

4. It is considered that the combination of D1 and D2 would not have led a skilled person to an immunisation method for ameliorating transplantation of porcine tissue. Consequently claims 1-15,20-23 are regarded as inventive.

ITEM VIII

5. However claims 7-15 are unclear as they do not necessarily relate to the same inventive concept as that covered by claims 1-6. The composition, as so broadly defined in these claims, would not have be used in the method covered by claims 1-6, in which case a different problem could be seen to be solved. However as the other possible uses of this composition are not found in the description an objection under Article 6 PCT must be made to these claims as they are not fully supported by the description their entire breadth.

6. Claim 20 is not fully supported by the description contrary to Article 6 PCT. It is considered that the application deals with porcine tissue being grafted. Claim 20 however fails to include this detail and thus suggests that method of treatment of any xenograft (from any other animal) may be ameliorated with porcine immunogen. Clearly this has not been shown and consequently the claim is not fully supported by the description.

CLAIMS

1. A method of improving tolerance to a xenograft comprising; immunising a mammal with an immunogen comprising at least one T- cell epitope and at least one B- cell epitope characterised in that said B- cell epitope is derived from at least one porcine polypeptide involved in mediating the rejection of said xenograft.

2. A method according to Claim 1 characterised in that said B-cell epitope is a peptide derived from at least one porcine polypeptide selected from; CD40; CD80; CD86 or VCAM.

3. A method according to Claim 1 or 2 characterised in that said peptide is selected from at least one peptide represented in Figure 22.

4. A method according to Claim1 or 2 characterised in that said peptide is selected from at least one peptide represented in Figure 24.

5. A method according to Claim1 or 2 chrarcterised in that said peptide is selected from at least one peptide represented in Figure 26.

6. A method according to Claims 1 – 5 characterised in that said T – cell epitope is derived from tetanus toxoid polypeptide.

7. A composition comprising an immunogen characterised in that said immunogen has at least one B- cell epitope and at least one T – cell epitope wherein said B – cell epitope is derived from at least one porcine polypeptide involved in mediating xenograft rejection.

8. A composition according to Claim 7 characterised in that said porcine polypeptide is expressed by vascular endothelial cells of said xenograft.

9. A composition according to Claims 7 or 8 characterised in that said B – cell epitope is derived from at least one porcine polypeptide selected from; CD40; CD86; CD80; VCAM.

10. A composition according to Claim 9 characterised in that said B- cell epitope is selected from at least one peptide as represented in Figure 22 .

11. A composition according to Claim 9 characterised in that said B- cell epitope is selected from at least one peptide as represented in Figure 24 .

12. A composition according to Claim 9 characterised in that said B- cell epitope is selected from at least one peptide as represented in Figure 26.

13. A compostion according to Claims 9 or 12 characterised in that said B- cell epitope is derived from the extracellular domain of CD86.

14. A composition according to Claims 7 - 13 characterised in that said T- cell epitope is derived from tetanus toxoid.

15. A composition according to Claims 7 - 14 characterised in that said composition further comprises a carrier capable of enhancing the immune response to said immunogen.

16. An antibody, or the effective part thereof, characterised in that said antibody is capable of distinguishing between porcine polypeptides according to Claims 7 – 15 and the homologous polypeptides of the mammal receiving said xenograft.

17. An antibody according to Claim 16 characterised in that said antibody is monoclonal.

18. An antibody according to Claims 16 or 17 characterised in that said antibody is modified with at least one detectable label.

19. A method to monitor the immune status of a mammalian recipient of a xenograft comprising:

i) removing a sample from a xenograft recipient to be tested;
ii) contacting said sample to the antibody according to Claims 16 - 18; and
iii) monitoring the expression of the porcine polypeptide according to Claims 4 –8.

20. A method to treat a mammal prior to receiving a xenograft comprising:

i) immunising a mammal with an immunogenic composition according to Claims 7 - 15;
ii) assessing the immune status of said mammal to said immunogenic composition;
iii) transplantation of said xenograft tissue/organ into a recipient mammal; and
iv) monitoring the rejection response to said xenograft.

21. A method according to Claim 20 characterised in that said xenograft is of porcine origin and said mammal is human.

22. A method according to Claim 20 or 21 characterised in that said xenograft is at least one vascularised graft and/or immunogenic porcine cell/tissue.

23. A method according to Claim characterised in that said xenograft is pancreatic islets.